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TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS WITH AZATHIOPRINE

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Translation of "Hatiful b'zavat admantit merhatit im azathioprine," Harefual, Vol. 86, No. 7, 1964, pp. 382-384

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16. Abstract A brief history of experiments on the use of azathioprine in the treatment of patients with systemic lupus erythematosus with kidney involvement has demonstrated azathioprine's effectiveness. Azathioprine has two main characteristics: immunologic and cytotoxic depression activity and anti-inflammation activity. In dosages of 2.5 mg/kg/day, azathioprine is tolerated well by patients, producing few side effects, possible depression of the marrow which is easily reversible, and no exhibition of teratogenic changes. Used in conjunction with steroids, it allows a reduction in steroid dosage, thereby reducing toxic side effects of the steroids. Discontinuation must be gradual to avoid aggravation of the disease.

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TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS WITH AZATHIOPRINE

E. Sharon

The treatment of systemic lupus erythematosus (SLE) was /382* greatly promoted by introduction of steroid treatment in this disease. The expected survival rate in patients improved by 80% in 3 years and 50% to 60% in 10 years [1]. The prognosis re- /383 mained poor in patients with diffuse lupus glomerulitis and with involvement of the central nervous system. The deficiency in kidney absorption remained the cause of death of the patients.

Autopsy results show that, in 75% of the SLE patients, the kidneys are diseased [2]. From the histological point of view, three forms are known: 1) the focal form -- there are changes only in part of the glomeruli area; 2) the diffuse form; 3) the membranous form.

The focal form does not progress to the other forms, which are more severe. The most severe is the diffuse form, which sooner or later inhibits the kidney's performance. A kidney biopsy is the only exact way to determine the form and the degree of involvement, because the urine sediment test does not show the histological results clearly [4]. Pollak [3] has found that, when the primary blood urea was less than 60 mg/100 ml, high dosages of corticosteroids (40 to 60 mg/day) caused a substantial improvement in lupus glomerulitis. With this dosage, the disease activity stopped, but the death rate remained at 42%.

Baldwin, in a 3-year follow-up in SLE patients with diffuse glomerulonephritis who were treated with steroids found that the death rate was 38%.

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* Numbers in the margin indicate pagination in the foreign text.

When mercaptopurine-6 was found to be a substance which depresses the creation of antibodies [6], the antimetabolic treatment of autoimmunological diseases was begun. Experiments were also performed with cyclophosphamide (Cytoxan) and chlorambucil (Libecran). The first experiments were on a small scale and were uncontrolled. The condition of two out of four patients having a nephritic syndrome as a result of SLE and not responding to steroid treatment [7] was improved after treatment with mercaptopurine.

Azathioprine (Imoran) (hereafter A.T.), which is a derivative of mercaptopurine-6, was administered in dosages of 1.9 to 4.3 mg/kg in an uncontrolled experiment [8] on 11 patients with lupus nephritis who did not respond to steroids. Four of them died, only one from problems with kidney absorption. A permanent clinical improvement was found in three patients, and two patients showed a temporary improvement. Five patients, three of them with uremia at the beginning, did not react.

In another experiment [9], SLE patients with kidney involvement were treated with A.T. after not responding to steroids or showing resistance to the medication. It was found that the kidney activity remained stable or improved, and that a histological examination of the kidney showed a decrease in the growth of glomerule cells and only the sclerosis level had increased.

In another work [10], a clinical and histological improvement in lupus glomerulonephritis with steroid treatment in a low dosage (less than 20 mg/100 ml) and with addition of A.T. was observed. In some cases a transfer from a severe and diffuse form to the less severe membranous form was observed in the histological examination with electron microscope as a result of the treatment.

The unpredictable course of SLE makes the planning of controlled treatment research on the effectiveness of the immunosuppressives difficult. It is desirable that such research be carried out with medical cooperation within centers and with a cautious and detailed follow-up. In the first published account of controlled research [11], 16 SLE patients were treated with prednisone and A.T. (2.5 mg/kg/day). The follow-up was continued from 1 to 4 years, and a comparison was made with 19 patients who were treated only with prednisone. Twenty-one patients were included in each group, but seven died during the first hospitalization as a result of damaged kidneys, damaged nervous system or a general infection, which implies that A.T. is not immediately effective in the acute stage of the disease. Six patients from the control group (without A.T.) died, three from kidney absorption deficiency, two from infection and one from hematological complications. There were no deaths in the group which was treated with A.T.

The major deficiency in this work is the lack of sufficient kidney biopsies. It was found that the use of A.T. led to the lowering of the prednisone dosage in the treatment, and, in seven out of 16 patients, allowed it to be stopped. Toxic side effects were few, and the depression of the marrow, if it appears, was always reversible with discontinuation of the medicine.

In another work, the short-term influence of A.T. on lupus nephritis was measured [12]. The patients were selected on the basis of immunologic systemic activity and the histological tests of the kidney before and after the experiment. The 16 patients were divided into two groups. In one group, the treatment began with a high dosage of steroids, which was gradually lowered to a maintenance dosage. The second group, in addition to this, was treated with A.T., 2 mg/kg/day. The clinical and morphological improvement was the same in both groups after 6 months of

treatment. A repeated kidney biopsy showed a regression in the activity of the disease, as compared to the situation before the treatment. The creatinine excretion remained stable or was improved, and there was a decrease in the protein level. It was concluded that A.T. does not contribute to the short-term effectiveness in the treatment of slight to moderate lupus nephritis when given in addition to a high dosage of steroids.

It was found [13] that a sudden discontinuation of A.T. in SLE patients, whose disease was stable, aggravated the condition in seven out of nine patients, and in only one out of seven patients in the control group, in which the treatment continued. The average time of the appearance of symptoms, which were generally difficult to detect, from the end of treatment was 90 days. One patient died from advanced kidney disease, in spite of treatment with high dosages of steroids and A.T. during the inflammatory stage of the disease, which was previously stable.

A.T. in dosages of 2.5 mg/kg/day is tolerated well by SLE patients. The toxic side effects are few and transient [14]. The depression of the marrow, which is the main toxic phenomenon, passes with a decrease of the dosage or discontinuation of the medication. In contract to many statements about the appearance of teratogenic changes in test animals under treatment with mercaptopurine, three pregnancies which ended with the birth of four normal babies were recorded in SLE patients under treatment with the medication [15]. The danger of tumor development, especially in relation to observations in kidney transplant patients [16], aroused an argument that is still unresolved, and it is the main deterrent against using this medication or similar medications in benign diseases [17].

Apparently, the A.T. has two main characteristics: immunologic and cytotoxic depression activity and anti-inflammation activity. It is still unclear which is the one that contributes

to the effectiveness of the treatment. The fact that the populations of small lymphocytes and plasma cells remain stable under medication and that there is no influence on the immunocompetence points to another characteristic that is not only immunosuppressive.

Despite the relatively wide use of A.T. in SLE and other diseases, it is too early to derive general conclusions on the activity of the medication and its long-term influence. Lately, some surveys were published on the data that has been accumulated up to now [18, 19]. In summary, there is a clear advantage of treating SLE patients with A.T. Its characteristics as a steroid substitute are impressive and allow lowering the steroid dosage required to overcome the disease activity during treatment, which results in fewer side effects, especially infection, and in a shortening of the hospitalization time when the disease is acute.

At the medical center of the University of New York, the standard approach is to use A.T. in SLE patients when: 1) the patient needs more than 15 mg prednisone per day for a long period of time; 2) the patient is in special danger because of the steroid treatment; 3) the patient suffers from severe complications of the disease, such as diffuse glomerulonephritis or involvement of the central nervous system. It is very important to remember that the effects of the medication might be delayed and that several weeks are needed to be sure of the effectiveness of the medication or to reveal toxic effects (especially leukopenia). A.T. has a stabilizing effect on the disease and, once a /384
clinical remission is reached, the treatment must continued for a long period. To avoid an acute aggravation of the disease, the discontinuation of the medication must be gradual.

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